Remarks

A Request for Continued Examination is made in this Reply to the Office Action dated December 15, 2006, (hereinafter "OA") and the Advisory Action of July 3, 2007 (hereinafter "AA").

Claims 30, 36, 44, 45, 67, 76-93 are pending in the application, with 30, 36, 67 and 87-93 being the independent claims. Claims 30, 36, 67, 77 and 78 are sought to be amended. New claims 79-93 have been added. Support for these amendments may be found, *inter alia*, at page 11, ¶ [0040], page 18, ¶ [0081] and page 19, ¶ [0082] and original claims 16 and 27. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendments and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. Request for Interview

Applicants have submitted a PTOL-413A form to request an interview before the issuance of a first Office Action on the merits. As required on the interview request form Applicants have indicated a time and date for the interview. If this time is not convenient for the Examiner, the Examiner is requested to contact the undersigned attorney and reschedule the interview for a mutually convenient time.

II. Rejections under 35 U.S.C. § 103

The Examiner has rejected claims 30, 31, 36, 44, 45, 55-57, 67, 68, 71 and 74-76 as allegedly being obvious over U.S. Patent No. 5,443,976 (hereinafter "the '976 patent") in view of U.S. Patent No. 4,849,352 (hereinafter the "the '352 patent") as evidenced by Harlow and Lane (*Antibodies*, Harlow, E. and Lane, D., eds., Cold Spring Harbor Laboratory Press, pp. 298-99) (1988) (hereinafter "Harlow") and Campbell (*Monoclonal and Immunosensor Technology*, Campbell, A., ed., Elsevier Science, pp. 288-91) (1991) (hereinafter "Campbell"). *See* OA at page 7, AA at page 2. More specifically, the Examiner alleges that one of ordinary skill in the art would have been motivated to combine teachings of antibody to scorpion venom *Centruroids noxius* taught by the '976 patent with the teachings of the '352 patent to produce more readily utilizable antibody to scorpion venom. OA at page 7. The Examiner asserts that the prior art teaches the use of ammonium sulfate precipitation for the production of antibody preparations and that "repeating the precipitation process as necessary is within the optimization of procedures" OA at page 5, AA at page 2. Applicants respectfully traverse this rejection

The factors to be considered under 35 U.S.C. § 103(a), are the scope and content of the prior art; the differences between the prior art and the claims at issue; and the level of ordinary skill in the pertinent art. *See Graham v. John Deere*, 86 S.Ct. 684 (1966) and MPEP §2141. This analysis has been the standard for 40 years, and remains the law today. *See KSR International Co v. Teleflex Inc.*, 127 S.Ct. 1727 (2007). The Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the cited art. *See In re Piasecki*, 745 F.2d 1468, 1471-72 (Fed. Cir. 1984). A *prima facie* case of obviousness cannot be established unless all of the claim elements are taught or

suggested by the cited references. *See In re Royka*, 490 F.2d 981, 984-85 (CCPA 1974); *see also In re Glaug*, 283 F.3d 1335, 1341-42 (Fed. Cir. 2002); *In re Rijckaert*, 9 F.3d 1531, 1533 (Fed. Cir. 1993). To establish a *prima facie* case of obviousness, it is not sufficient to merely combine individual elements known in the prior art if the results would not have been predictable to one of ordinary skill in the art. *See* Examination Guidelines at page 57529. Furthermore, one cannot simply ignore teachings in the prior art that would lead ordinary artisan away form making certain combinations. *United States v. Adams*, 383 U.S. 39, at 51-52 (1966). If one (or more) of the references teaches away from the combination, it is improper to combine the references. *See* MPEP § 2145(X)(D)(2).

In this case, claims 30, 36, 44, 45, 67 and 76-93 are directed to a pharmaceutical composition comprising polyclonal $F(ab')_2$ antibody fragments *substantially free from albumin and whole antibodies and substantially free of pyrogens,* wherein the antibodies bind to antigenic molecules of scorpion venom from the species *Centruroides limpidus.* The Examiner asserts that "the '976 patent teaches IgY polyclonal antibodies to a scorpion venom, *Centruroids noxius*." OA at page 5, and AA at page 2. Although the Examiner acknowledges that the '976 patent does not teach $F(ab')_2$ fragments, she asserts that one of ordinary skill in the art would have been motivated to pepsin digest the IgY antibody of the '976 patent in order to obtain $F(ab')_2$ fragments. *See* OA at page 6, AA at page 2. Applicants respectfully traverse this rejection.

The '976 patent and the '352 patent, alone or in combination, do not teach all the claimed elements, and actually teach away from the compositions of the presently-

pending claims. Thus, the Examiner's burden of establishing a *prima facie* case of obviousness has not been satisfied.

1. The '976 patent

A person of ordinary skill in the art would not have been motivated to combine the disclosures of the '976 patent and the '352 patent to arrive at the presently-claimed invention because the '976 patent teaches away from making $F(ab')_2$ antibody fragments for use as antivenom. Furthermore, even if a person of ordinary skill in the art did combine these two references, he or she would not arrive at the present invention because the '976 patent is missing at least two elements required by presently-pending claims 30, 36, 44, 67 and 76-93.

A. The '976 patent does not disclose all the elements of the present invention

The '976 patent discloses the production of separate antivenins against *Centruroids suffusus, Centruroides noxius* and *Centruroides sculpturatus* individually. The '976 patent also discloses the steps of detoxifying the venom, injecting the venom into chickens, and collecting the eggs to obtain the antibody followed by affinity purification of the antibody. *See* the '976 patent, col. 62, ll. 15-57. The '976 patent does not teach making an antivenin against antigenic molecules of scorpion venom from the species *Centruroides limpidus.* As admitted by the Examiner, the '976 patent does not teach $F(ab')_2$ antibody fragments. *See* AA, page 2. Thus, the '976 patent is missing (1) antivenins against scorpions within the species *Centruroides limpidus*, and/or (2) polyclonal $F(ab')_2$ antibody fragments free from albumin and whole antibodies and

substantially free of pyrogens, both of which are required by the presently-pending claims 30, 36, 44, 67, and 76-93.

B. The '976 patent teaches away from making F(ab')$_2$ antibody fragments for use as an antiveninin

A person of ordinary skill in the art would not have been motivated to combine the disclosures of the '976 patent and the '352 patent to arrive at the presently-claimed invention because the '976 patent teaches away from making F(ab')$_2$ antibody fragments for use as antivenom.

The '976 patent discloses a method of making and purifying antivenoms, preferably by immunizing chickens, collecting IgY from egg yolk, and purifying the venom specific IgY using an antigen matrix. *See* the '976 patent, col. 12, l. 61 - col. 13, l. 27. As discussed in the "Background" section of the present specification, it was known at the time of filing that F(ab')$_2$ antibody fragments antibody fragments are made by digesting whole antibodies with the enzyme pepsin. S*ee* Spec. at ¶ [0008]. Although the '976 patent does not discuss F(ab')$_2$ antibody fragments, it does make reference to the problems associated with antibody-based antivenoms generated using pepsin digestion:

> [t]he potency of individual lots of antivenoms will vary because of two principal factors. First, because the whole antisera or immunoglobulin fractions used and the specific antibody titer per unit volume will vary from animal to animal and from day to day, the amount of venom-reactive antibodies will differ from preparation to preparation. Second, *refinement procedures such as ammonium sulfate precipitation and pepsin digestion can reduce the yield of active antibody, causing variations in the titer of active ingredient per unit volume.* These difficulties are exacerbated when antivenom is raised against a set of venoms in order to treat a range of species.

The '976 patent col. 6, ll. 20-32 (emphasis added). Because pepsin digestion can reduce active antibody yield and cause other problems, the ordinary artisan would not have been motivated to use pepsin digestion (which produces $F(ab')_2$ antibody fragments) to produce antibody-based antivenoms. The '976 patent also highlights the fact that problems associated with pepsin digestion (and ammonium sulfate precipitation) of antibodies are exacerbated when an antivenom is produced against venoms of multiple species. *See* the '976 patent col. 6, ll. 20-32 Thus, the '976 patent teaches away from using pepsin digestion and/or ammonium sulfate precipitation of antibodies for use as an antivenom, particularly against a range of species, as recited in the presently-pending claims.

2. The '352 patent

A. The '352 patent does not disclose all the elements and teaches away from the present invention

As discussed above, claims 30, 36, 44, 45, 67 and 76-93 are directed to a pharmaceutical composition comprising polyclonal $F(ab')_2$ antibody fragments *substantially free from albumin and whole antibodies and substantially free of pyrogens,* wherein the antibodies bind to antigenic molecules of scorpion venom from the species *Centruroides limpidus.* The Examiner asserts that the '352 patent "teaches a pharmaceutical composition comprising polyclonal $F(ab')_2$ antibodies that binds to any antigen." OA at page 5, AA at page 2. The Examiner also asserts that it would have been obvious to one of ordinary skill in the art at the time application was filed to pepsin digest antibodies and purify these antibody fragments with ammonium sulfate, and

further to apply this technique to the IgY antibodies of the '976 patent. OA at page 6, AA at page 2. Applicants respectfully disagree.

First, the '352 patent does not disclose the production of antibodies and isolation of antibody fragments directed against the scorpion venom from the species *Centruroides limpidus*. Second, the '352 patent discloses a process of isolating $F(ab')_2$ fragments by using antigen immobilized affinity columns, and repeatedly teaches away from using ammonium sulfate precipitation process. *See* the '352 patent eg col. 6, ll. 3-5; col. 6, ll. 53-55. More specifically, the '352 patent states, "applicants have negated the need for the ammonium sulfate precipitation procedures . . ." The '352 patent, col. 6, ll. 53-55. An affinity chromatography column binds whole antibodies as well as $F(ab')_2$ fragments, and cannot distinguish between the two structures. Thus, the bound molecules of the '352 patent are mixtures containing whole antibodies and $F(ab')_2$ fragments therefore are not "substantially free from albumin and whole antibodies and substantially free of pyrogens," as required by the presently-pending claims.

The '352 patent states that commercial antivenoms such as MONOVALANT BOTHROPS, ANTICROTALIC and CENTIVIPERIN are made by pepsin digestion followed by ammonium sulfate precipitation. The '352 patent, col. 3, ll. 1-15. However, the '352 patent explains that such enzyme digestion and ammonium precipitation procedures do not remove all foreign proteins from horse serum derived antivenins. The '352 patent, col. 3, ll. 1-15. Consequently, these materials sometimes cause severe allergic reactions for unknown reasons, possibly related to the presence of anticomplement activity (*i.e.* whole antibodies) or lack of purity. *Id.*

Allergic reactions are extremely undesirable when administering pharmaceutical compositions. A treatment protocol often requires large quantities and repeated doses of the antivenin to be effective, with each additional dose, the risk of allergic reaction increases. Consequently, a person of ordinary skill in the art would have been led away from applying such processes due to the likelihood of the resulting antivenin containing dangerous contaminants. Thus, a person of ordinary skill in the art at the time of filing would not have been motivated to use pepsin digestion and ammonium sulfate precipitation, as disclosed in the '352 patent, to produce a composition comprising polyclonal $F(ab')_2$ antibody fragments substantially free from albumin and whole antibodies and substantially free of pyrogens, as recited in the presently-pending claims.

3. Harlow and Campbell do not rectify the shortcomings of the '976 patent and/or the '352 patent

A. Harlow

The Examiner asserts that Harlow teaches that "repeating the precipitation process as necessary is within optimization of procedures." AA page 2. Applicants respectfully disagree with the Examiner's assessment, and assert that Harlow does not disclose or suggest producing $F(ab')_2$ antibody fragments against the species *Centruroides limpidus* according to the process recited in the presently-pending claims.

In addition to requiring that the antibody fragments are substantially free from albumin and whole antibodies and substantially free of pyrogens, claims 30, 36, 44, 45, 67 and 76-85 also require that the ammonium sulfate precipitation procedure utilize a two-step purification process. Specifically, the claims require that the initial step utilizes

an ammonium sulfate at a concentration of about 16% to about 22% weight, and that the final step uses an ammonium sulfate at a concentration of about 32% to about 38% weight by volume to obtain antibody fragments from albumin and whole antibodies and substantially free of pyrogens.

In contrast, Harlow discloses an initial precipitation step of about 25% weight by volume solution (as calculated by the Examiner). *See* OA at page 6, AA at page 2. That step is followed by an antibody precipitation step using a concentration of ammonium sulfate of 38.5% weight by volume. In both process steps, the ammonium sulfate concentrations of Harlow fall outside the ammonium sulfate ranges recited in the presently-pending claims. Furthermore, there is nothing in Harlow to suggest using ammonium concentrations within the ranges cited in the presently-pending claims.

In an effort to overcome the shortcomings of Harlow, the Examiner asserts that adjusting the ammonium sulfate concentration to fall within the ranges recited in the presently-pending claims would have been possible with routine optimization. *See* AA page 2. Applicants disagree with the Examiner's assessment because the ordinary artisan would only be motivated to optimize a procedure if that procedure produces a predictable result.

As discussed above, Harlow discloses antibody precipitation using ammonium sulfate, and recognizes that:

> [o]ne disadvantage of ammonium sulfate precipitation is that the resulting antibodies will not be pure. They will be contaminated with other high-molecular-weight proteins, as well as proteins that are trapped in the large flocculant precipitates. Therefore ammonium sulfate is not suitable for a

> single-step purification but must be combined with other methods if pure antibodies are needed.

See page 298 (emphasis added). The ordinary artisan would not have been motivated to use a process that was known to result in an impure antibody composition to arrive at the $F(ab')_2$ antibody fragment composition that is substantially free from albumin and whole antibodies and substantially free of pyrogens of the presently-pending claims. Further, there was nothing to suggest that changing parameters of Harlow to those recited in the presently-pending claims would have solved the problems with ammonium sulfate precipitation and result in a pure product.

Additionally, Harlow does not disclose making or using $F(ab')_2$ antibody fragments against *Centruroides limpidus* as also required by the presently-pending claims.

B. Campbell

Campbell also does not cure the defects associated with the '976 patent, the '352 patent and/or Harlow because it does not disclose or suggest making or using antibody fragments against *Centruroides limpidus,* as required by the presently-pending claims. Instead, Campbell is cited by the Examiner to provide a weight volume designation for ammonium sulfate for the purpose of making calculations. OA at page 6, AA at page 2.

Campbell also teaches away from the use of ammonium sulfate precipitation. More specifically, Campbell teaches that large-scale commercial production would move away from ammonium sulfate precipitation procedures due to the unacceptable high cost. *See* page 288, 1st paragraph. Campbell does not use a two-step ammonium sulfate

precipitation process and only considers using the ammonium sulfate step as an initial concentration step. *See* Campbell page 289, table 10.1. After the initial concentration step with ammonium sulfate, the antibodies are further purified using DEAE or Mono Q chromatography, followed by protein A or protein G purification and finally by affinity purification. According to Campbell, one or more additional process steps are required before the antibody is pure. *See* Campbell page 289, table 10.1. The reference also points out that there are occasions where the use of ammonium sulfate precipitation results in a loss of antibody titer, and in that event other purification procedures should be considered. *See* page 291. Thus, a person of ordinary skill in the art would not have been motivated by Campbell to use ammonium sulfate precipitation to arrive at the $F(ab')_2$ antibody fragment composition that is substantially free from albumin and whole antibodies and substantially free of pyrogens of the presently-pending claims because of the potential impurities and loss of antibody function.

4. A composition comprising $F(ab')_2$ antibody fragments against Centruroides limpidus would not have been obvious in view of the prior art

Presently-pending claims 30, 36, 44, 45, 67 and 76-93 are directed to a composition comprising polyclonal $F(ab')_2$ antibody fragments . . . that bind to a purified molecule or mixture of antigenic molecules found in the venom of a scorpion of the species *Centruroides limpidus.*

A person of ordinary skill in the art at the time of filing would not have predictably arrived at an antivenin composition against a range of species, as recited in the presently-pending claims, because such a combination would not have even been

obvious to try in light of the prior art. *See Ex Parte Kubin*, 83 USPW2d 1410 (Bd. Pat. App. & Int. 2007).

The present invention is directed to a composition comprising a $F(ab')_2$ antibody fragments substantially free from albumin and whole antibodies and substantially free of pyrogens, wherein said $F(ab')_2$ antibody fragments bind to a purified molecule or a mixture of antigenic molecules found in the venom of a scorpion of the species *Centruroides limpidus*. The species *Centruroides limpidus* comprises the sub-species *C. limpidus limpidus*, *C. limpidus tecomanus* and *C. suffussu suffussus*. None of the cited references discloses the use of venom from the scorpion species *Centruroides limpidus* to produce an antivenin.

The '976 patent states that there are at least 650 different species of scorpions. col. 2, ll. 15-27. Because there are at least 650 species of scorpions, the possible number of scorpion venom combinations to produce an antibody composition in an animal is virtually infinite. Thus, it would not have been obvious to try to make an antivenin against *Centruroides limpidus* in light of the myriad possible combinations. Additionally, a person of ordinary skill in the art would not have had a reasonable expectation of success that combining the venoms as an immunogen would lead to a successful antivenin. The '976 patent col. 6, ll. 30-33.

As such, Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness because it would not even have been obvious to try to make an antivenin against the scorpion species *Centruroides limpidus* in light of the cited

references. Applicants respectfully request reconsideration and withdrawal of this rejection.

Conclusion

Applicants submit that the Examiner has failed to make a *prima facie* case of obviousness based on the cited references. The references, alone or in combination, do not disclose all the elements of the presently-pending claims. Specifically, the references do not teach making or using composition comprising $F(ab')_2$ antibody fragments against *Centruroides limpidus*, as recited in the presently-pending claims. The references also do not disclose the claimed element of using a two-step purification process falling within the specifically claimed ammonium sulfate concentration ranges to produce a pure antibody composition. In addition, consideration of the references in their totality reveals that each of the references indicate that the use of ammonium sulfate precipitation will not yield a pure antibody product, and that this procedure can also lead to a loss of antibody activity. Thus, the combination of the cited references is not proper because they that teach away from the present invention.

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all currently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will

expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Reply is respectfully requested.

Respectfully submitted,

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